

SPECIFICATIONS



To Whom It May Concern:

Be it known that I, Philip Chidi Njemanze, being a citizen of Nigeria, and residing in Owerri, Imo State, Nigeria with post office address of: No 1 Uratta/MCC Road, Owerri, Imo State, Nigeria, P. O. Box 302, and email: philip.njemanze@chidicon.com have invented a new and useful improvement in

Apparatus and method for Hypothermia and Re-warming by altering the temperature of the cerebrospinal fluid in the brain

CROSS-REFERENCE TO RELATED APPLICATION

US PATENT DOCUMENTS

5486208	Jan., 1996	Ginsburg	607/106
6558412	May, 2003	Dobak, III.	607/105
6197045	Mar., 2001	Carson	607/104
6620187	Sep., 2003	Carson et al.	607/104
6547811	Apr., 2003	Becker et al.	607/105
6581400	Jun., 2003	Augustine et al.	62/259.3
6126680	Oct., 2000	Wass	607/96
5916242	Jun., 1999	Schwatz	607/113
6217552	Apr., 2001	Barbut	604/113
6660026	Dec., 2003	Larnard et al.	607/104
6622725	Sep., 2003	Fisher et al.	128/204.21
6929656	Aug., 2005	Lennox	607/105

US PATENT APPLICATION PUBLICATIONS

2002/0198579	Dec. 2002	Khanna	607/104
2004/0143312	Jul., 2004	Samson et al.	607/105
2004/0138728	Jul., 2004	Wong et al.	607/105

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR

DEVELOPMENT Not applicable

REFERENCE TO MICROFICHE APPENDIX Not applicable

BACKGROUND OF THE INVENTION

The present invention generally relates to the selective modification and control of a patient's body temperature, specifically to the altering of the temperature of the cerebrospinal fluid that circulates within the brain.

Hypothermia is a clinical condition of abnormally low body temperature generally characterized by a core body temperature of 35 degree Celcius or less. By severity, mild hypothermia describes a body core temperature within the range of 32 degrees Celcius to 35 degrees Celcius, moderate between 30 degree Celcius to 32 degrees Celcius, severe between 24 degrees Celcius to 30 degrees Celcius, and profound - a body temperature of less than 24 degrees Celcius. These are relative distinctions and definition may vary widely in literature. However, in severe hypoxic-ischemic injury, animal models suggest that the optimum temperature is between 32 degrees Celcius and 34 degrees Celcius as disclosed in an article by Colbourne F, Sutherland G, Corbett D., entitled "Posttraumatic hypothermia: a critical appraisal with implication for clinical treatment", published in *Mol Neurobiol.*, vol. 14, pp. 171-201 (1997). As body temperature falls below 34 degrees Celcius, there is an increased risk of infection, coagulopathy, thrombocytopenia, renal impairment, and pancreatitis as disclosed by Schubert A., in an article entitled "Side effects of mild hypothermia", published in *J Neurosurg Anesthes* vol. 7, pp. 139-147 (1995); and also by Metz C, Holzschuh M, Bein T, et al., in an article entitled "Moderate hypothermia in patients with severe head injury: cerebral and extracerebral effects", published in *J Neurosurg.*, vol. 85, pp. 533-541 (1996).

To be effective, hypothermia needs to be achieved within 2-6 hours of severe hypoxic-ischemic injury possibly begun in the ambulance as disclosed in an article by

Bernard SA, Gray TW, Buist MD, et al., entitled "Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia", published in N Engl J Med., vol. 346, pp. 557-563 (2002). The duration of hypothermia for hypoxic-ischemic injury depends on the severity of the injury and the delay before the hypothermia is achieved. Within limits, a more severe injury or a longer delay can be compensated for by cooling for longer as disclosed in an article by Gunn AJ., entitled "Cerebral hypothermia for prevention of brain injury following perinatal asphyxia", published in the Curr Opin Pediatr vol. 12, pp. 111-115 (2000). What is therefore required is a device that will achieve hypothermia in the shortest possible time.

Conversely, hyperthermia is a clinical condition of abnormally high body temperature, due to exposure to a hot environment or surroundings, overexertion, or fever. Body core temperatures may range from 38 degrees Celcius to 41 degree Celcius due to conditions such as fever, and may be substantially higher in cases of exposure and overexertion. Hyperthermia is a serious and potentially fatal condition. The common causes of hyperthermia are systemic inflammatory response, sepsis, stroke, or other brain injury. The mechanisms of the effect of the hyperthermia on the brain remains to be fully elucidated, however, there is evidence to indicate that even mild increases in temperature may contribute to neurological deficits. Hyperthermia also increases the cerebral metabolic rate and may deplete cell energy stores.

Following hypothermia there is rewarming to normal body temperature. Induced hypothermia has been used clinically for neuroprotection during cardiovascular surgery, severe cardiac conditions (cardiac arrest, myocardial infarction), neurosurgery, head trauma, subarachnoid hemorrhage, spinal trauma, stroke, thoracic aortic aneurysm repair,

and liver transplantation. The mechanisms of action of clinical hypothermia may include blunting of post-insult release of neurotransmitters such as glutamate, reduction of cerebral metabolic rate, moderation of intracellular calcium, prevention of intracellular protein synthesis inhibition, and reduction of free radical formation as well as other enzymatic cascades and even genetic responses. For example, it has been demonstrated that hypothermia produces an attenuation of the release of excitatory neurotransmitters in meningitis and suggest that this treatment may attenuate neuronal stress as disclosed by Irazuzta JE, Olson J, Kiefaber MP, Wong H., in an article entitled "Hypothermia decreases excitatory neurotransmitter release in bacterial meningitis in rabbits", published in *Brain Res.*, vol. 847, pp. 143-148 (1999).

In the clinical setting, methods of induced hypothermia could be classified as whole body and regional hypothermia, invasive and noninvasive methods. Whole body hypothermia is usually invasive, not only takes a significant amount of time, but also subjects the patient to deleterious effects of hypothermia including cardiac arrhythmias, coagulation problems, increased susceptibility to infections, and problems of discomfort such as profound shivering. One way to induce whole body hypothermia is to externally cool the blood and pump it back to the patient using a bypass machine. This method is an extremely invasive procedure that subjects vast quantities of the patients' blood to pumping for an extended length of time. Such external pumping of blood may be harmful to the blood, and continued pumping of blood into a patient for extensive periods of time, for example, more than one or two hours, is generally avoided. During such procedures anticoagulants for example, heparin may be used, to prevent clotting which may present other undesirable consequences in victims of cerebrovascular accidents.

Other means of inducing hypothermia which do not require external pumping including the use of catheter has been proposed. For example, U.S. Pat. No. 5,486,208, to Ginsburg, describes a catheter that is inserted into a blood vessel and a portion of the catheter heated or cooled, transferring heat to the patient's blood and thereby affecting the overall body temperature of the patient. The U.S. Patent Application No. 2004/0138728 to Wong, describes inserting an elongated device into a lateral ventricle or other space of a brain; inflating a balloon disposed at an end of the device with a fluid; and controlling an internal temperature of the brain by circulating the fluid within the said balloon. The U.S. Patent No. 6,929,656 to Lennox describes an apparatus including a brain-cooling probe and a control console that cools the brain by withdrawing a small amount of cerebrospinal fluid from a ventricle into a cooling chamber located ex-vivo, and after cooling the cerebrospinal fluid it is reintroduced back into the ventricle. The U.S. Patent No. 6,217,552 to Barbut describes a device with two elongated catheters, a pump, a refrigeration system and a manometer. The cerebrospinal fluid is aspirated from the first catheter to the pump, cooled to below body temperature, and returned to the second catheter. The device is used for treatment of patients with spinal trauma undergoing aortic surgery. The US Patent 6,660,026 to Larnard et al discloses a multi-tipped cooling probe for the brain. The U.S. Patent Application 2004/0143312 describes a catheter for heat exchange apparatus which reside inside the catheter body for selectively altering the temperature of fluid that flows through the catheter shaft. The U.S. Patent Application 2002/0198579 to Khanna discloses a selective brain and spinal cord hypothermia method and apparatus for surgical use. One advantage of such devices and methods is that, they may avoid the problems associated with external pumping of blood, however, they

methods are still invasive and do not eliminate the difficulties that arise when the entire body is subjected to hypothermia particularly infection of blood.

Variations of balloons capable of acting as ongoing heat transfer balloons by the continual flow of heat transfer medium through the balloon have also been introduced. U.S. Patent No. 6,558,412 to Dobak III, describes a flexible catheter that is inserted through the vascular system of a patient to place the distal tip of the catheter in an artery feeding the selected organ. A compressed refrigerant is pumped through the catheter to an expansion element near the distal tip of the catheter, where the refrigerant vaporizes and expands to cool a flexible heat transfer element in the distal tip of the catheter. The heat transfer element cools the blood flowing through the artery, to cool the selected organ, distal to the tip of the catheter.

There have been attempts to achieve regional cerebral hypothermia, by directly cooling the surface of the head. For example, by placing the head in a cooled helmet or shroud, or even injecting a cold solution into the head region. U.S. Patent 6,581,400 to Augustine et al., describes an apparatus for convectively and evaporatively cooling a patient's head. The apparatus includes an upper sheet and a base sheet that are attached at a plurality of locations to form a convective device adaptable to the patient's head. Pressurized air is distributed throughout the convective device and flows to the patient's head through the apertures in the base sheet. U.S. Patent 6,126,680 to Wass discloses a method and apparatus for convective cooling of the brain in which cooled air is passed over a patient's head resulting in convective cooling of the patient's brain. The convective brain cooling apparatus comprises an air diffusing coverlet adapted to interface with an air cooling device and a coverlet capable of surrounding the patient's head and/or neck

region. The method may also include the additional step of selectively controlling cerebral blood flow and/or cerebral metabolism to further cool the brain or to maintain the brain in a hypothermic state relative to the patient's core temperature. However, the insulating qualities of the skull make it difficult to effectively lower brain core temperature, and the blood flow that may fail to provide sufficient heat transfer circulation to the brain itself when the surface of the head is cooled. Patients usually would require general anesthesia, in order to tolerate immersion or direct exposure of the head to a cold solution or cooling surface.

The use of contact pad systems such as that disclosed in U.S. Patent No. 6,197,045, to Carson and U.S. Patent No. 6,620,187 to Carson et al., for selectively cooling and/or heating bodily tissue is known. In such systems a fluid, e.g. water or air, is circulated through one or more pads to affect surface-to-surface thermal energy exchange with a patient. Cooling using external methods can lower the temperature of these oxygen-sensitive organs but only very slowly at rates of less than 0.05 degrees Celcius/minute (only 3 degrees Celcius/hr). In critical conditions there may be loss of pulse or inadequate perfusion, as a results core organs cools via direct tissue thermal conduction. Unfortunately, the speed of cooling with these techniques is too slow to prevent lethal outcome due to ischemic reperfusion injury to vital organs, including the heart and brain.

To overcome these limitations, U.S Patent No. 6,547,811 to Becker et al., provides for the application of phase-change particulate slurry cooling systems, equipment, and methods designed for cooling patients rapidly and safely. However, the '811 patent describes an invasive method for delivery of slurry for cooling of the brain.

According to the '811 patent, the operator first identifies the region of the carotid artery and the jugular vein in the neck. The skin is punctured with a needle and a catheter is inserted into the pericarotid region of the soft tissue of the neck. The external portion of the catheter is attached to a syringe containing the slurry. A specified volume of slurry is then injected into the soft tissues of the neck in the vicinity of the carotid artery and the jugular vein.

Rather than cooling the brain by the relatively slow heat conduction through the low heat conductivity of the bony skull and hair covering the head, U. S. Patent No. 5,916,242 to Schwartz describes the use of a light weight, easily applied neck encircling collar in firm contact with the soft tissue of the neck, and particularly in good thermal contact with the carotid arteries traversing the neck. A coolant flowing through channels embedded in the collar rapidly cools the blood flowing through the carotid arteries which branch into blood vessels throughout the brain providing vascular access and attendant rapid internal cooling throughout the brain.

In view of the foregoing, it may be appreciated that medical applications of hypothermia are ever increasing. By way of example, hypothermic devices may be utilized in early therapy to reduce neurological damage incurred by stroke and head trauma patients. Additional applications include selective patient heating/cooling during surgical procedures such as cardiopulmonary bypass operations.

As these and other medical applications have evolved, the inventor has recognized the desirability of enhancing the flexibility, predictability, responsiveness, and portability of hypothermic devices. Specifically, while known heating/cooling devices have proven effective for many applications, the inventor has recognized that additional performance

objectives and potential applications can be realized via the implementation of further improved thermoregulatory systems and associated methodologies based on new insights into pathophysiological mechanisms. Particularly, the inventor makes a principle departure from prior art by focusing on cooling the cerebrospinal fluid (CSF) bathing the brain centers of thermoregulation and thereby altering the central and peripheral afferents to neurons of the anterior and posterior preoptic hypothalamus and hence centrally resetting the body temperature to the desired level. Other design considerations include, integrating the device with other neurointensive care procedures without increasing the invasiveness of use of hypothermia in the clinical and emergency care settings.

In most cases, prior art lacks flexibility and portability and their application requires use in a controlled clinical setting. This limits their use particularly at sites of accidents by emergency rescue teams, as a result, hypothermia is usually applied much later on arrival to specialized centers with a controlled clinical environment after considerable damage has been done and efforts aimed at neuroprotection at such a late stage might be least rewarding. What is then required is a flexible and portable system easy to use during transportation of the victims from the site of the accident to the hospital.

In most instances the application of hypothermia according to the teachings of prior art requires specialized skills of the attending medical personnel or surgeon. This limits the scope of application to only selected centers in highly industrialized countries. What is therefore required is a device and method that could easily be carried out by most doctors and emergency personnel with general training and some surgical skills close to the site of a road traffic accident or after a natural disaster such as after an earthquake or

hurricane.

Prior art in most cases is highly invasive with serious adverse effects. The risk benefit analysis does not permit use in many instances where application of hypothermia could have otherwise been useful. What is therefore required is a less noninvasive method of hypothermia.

Prior art requires extensive expensive equipment usually requiring trained personnel. This limits there availability in remote centers where there are first responders to accidents. What is therefore required is simple equipment that is affordable to remote centers.

Prior art lacks specificity in operational mechanism. Prior art focuses on cooling/heating blood or tissue surrounding major vessels. This approach is countered by the body's own mechanisms of thermoregulation and therefore is rendered ineffective or achieves very minimal effects at the brain sites of regulation even during extensive high risk whole body exposures. What is required, therefore, is a method with high specificity, acting directly at brain centers by thermal exchange with the CSF, reducing cerebral metabolic rate, ~~and~~ improving energy stores and resetting thermoregulation.

Prior art based on cooling whole blood exposes vital organs to metabolic mismatch, between metabolic rate and optimal temperature for enzymatic and hormonal processes, as a result several enzymatic cascades are shut down which maybe vital for critical processes in the human body and hence the adverse effects. What is required is a method that centrally alters metabolic rate in synchrony with thermoregulation, such that the body physiologically resets the level of hormonally and enzymatically dependent processes to the level of temperature permissible.

Prior art undesirably cools other vital organs such as the lungs and thereby promoting the growth of infection, as a result, pneumonia is a frequent complication of hypothermia. What is required is a method that avoids undesirable cooling of other organs.

Prior art usually involves two separate phases of cooling and rewarming with elaborate distinct methods, usually requiring switching devices. What is required is a device that integrates both the cooling and rewarming phases into a simple two-step procedure without switching of apparatus.

Prior art lacks dynamic responsiveness to intensive care nursing needs considering variations in other vital signs such as for mean arterial blood pressure (MABP), end-tidal partial pressure of carbon-dioxide (PCO_2), mean cerebral blood flow velocity (MCBFV), and intracranial pressure (ICP). As a result the level of hypothermia using prior art is not necessarily responsive to vital signs status of the patient but is decided empirically. The rationale for a dynamic responsive system is best illustrated with the hemodynamic status after head injury. In cases of head injury ICP is the pivotal determinant of cerebral blood flow (CBF) because of its influence on the cerebral perfusion pressure (CPP) (defined as the MABP minus the ICP) as described by Aaslid R. in an article entitled "Cerebral hemodynamics", in a book by Newell D. W. et al. (ed.) entitled "Transcranial Doppler", published by Raven Press, New York: p. 49 (1992). Rise in cerebral perfusion pressure within the operative range of cerebral autoregulation results in compensatory active vasoconstriction to maintain a stable cerebral blood flow. The vasoconstriction leads to a decrease in cerebral blood volume and thereby to a decrease in intracranial pressure, as described by Rosner M., in an article entitled

"Pathophysiology and management of increased intracranial pressure", in a book "Neurosurgical intensive care" by Andrews B. T. (ed.), published by McGraw Hill Inc., New York: pp. 57-112 (1993). Below the lower cerebral autoregulatory limit or with autoregulatory failure in some patients after head injury, an increase in cerebral perfusion pressure will result in passive vasodilatation which will increase the cerebral blood volume and therefore the intracranial pressure. In this situation of cerebral autoregulatory failure, cerebral blood flow will vary with cerebral perfusion pressure, and a stable blood flow can no longer be maintained. An index comparing arterial blood pressure and intracranial pressure, the PRx, has been described by Czosnyka M., et al., disclosed in an article entitled "Continuous assessment of the cerebral vasomotor reactivity in head injury", published in Neurosurgery, vol. 41, pp. 11-17 (1997). PRx illustrates the correlation between arterial blood pressure and intracranial pressure. If intracranial pressure follows arterial blood pressure in a parallel fashion, there is a good correlation, and the PRx index is positive. On the other hand, if an arterial blood pressure increase causes vasoconstriction (that is, pressure autoregulation is preserved), a reduction in cerebral blood volume, and a decrease in intracranial pressure, the positive correlation will be lost; in this case the PRx will approach zero or even become negative, indicating well preserved cerebrovascular reactivity. The PRx index has been validated and it was further advocated that dynamic cerebrovascular autoregulation be measured using a moving correlation coefficient between arterial blood pressure and cerebral blood flow velocity, the Mx, as disclosed by Lang EW, Lagopoulos J, Griffith J, et al., in an article entitled "Cerebrovascular reactivity testing in head injury: the link between pressure and flow", published in J Neurol Neurosurg Psychiatry, vol. 74, pp. 1053-1059 (2003). What

is required is a system of body temperature cooling that is fully integrated with other vital signs and functions in a dynamic servo-feedback and feed-forward loop that could be used with a computerized algorithm. This will permit that the level of hypothermia is decided based on changes in vital signs status.

Prior art provides transient beneficial effects of hypothermia which easily reverses after a comparatively short duration. Therapeutic hypothermia maintains the ICP at lower levels during the cooling phase, but once patients were rewarmed, the ICP elevated to levels of normothermic patients as disclosed by Slade J, Kerr ME, Marion D., in an article entitled "Effect of therapeutic hypothermia on the incidence and treatment of intracranial hypertension", published in *J Neurosci Nurs*, vol. 31, pp. 264-269 (1999). Others have shown that hypothermia reliably reduced intracranial pressure as disclosed in articles by Jiang J, Yu M, Zhu C., entitled "Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases", published in *J Neurosurg*, vol. 93, pp. 546-549 (2000); by Shiozaki T, Hayakata T, Taneda M, et al., entitled "A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure", published in the *J Neurosurg*, vol. 94, pp. 50-54 (2001); by Clifton GL, Miller ER, Choi SC, et al., entitled "Lack of effect of induction of hypothermia after acute brain injury", published in *N Engl J Med*, vol. 344, pp. 556-563 (2001); by Iida K, Kurisu K, Arita K, Ohtani M., in an article entitled "Hyperemia prior to acute brain swelling during rewarming of patients who have been treated with moderate hypothermia for severe head injuries", published in *J Neurosurg*, vol. 98, pp. 793-799, (2003). However, these effects tend to reverse on rewarming. What is therefore required is a method that is safe for long

duration use and could be sustained for the entire period of treatment and rehabilitation.

Prior art does not combine the benefits of CSF drainage with the added benefit of neuroprotection with hypothermia. CSF drainage is a first line treatment used to manage severely elevated intracranial pressure ($> \text{ or } = 20 \text{ mm Hg}$) and improve outcomes in patients with acute head injury. However, CSF drainage alone provides a transient decrease in intracranial pressure without a measurable improvement in other indices of cerebral perfusion as disclosed by Kerr EM, Marion D, Sereika MS, in an article entitled "The effect of cerebrospinal fluid drainage on cerebral perfusion in traumatic brain injured adults", published in *J Neurosurg Anesthesiol*, vol. 12, pp. 324-333 (2000). Moreover, it has been demonstrated that hypothermia treatment significantly reduces excitatory amino acid and NO_2 concentrations, a finding which was associated with an improvement in cerebral perfusion pressure and oxygen saturation of the jugular venous blood (SjO_2) as disclosed by Yamaguchi S, Nakahara K, Miyagi T, et al., in an article entitled "Neurochemical monitoring in the management of severe head injured patients with hypothermia", published in *Neurol Res*, vol. 22, pp. 657-664, (2000). What is therefore required is a method that combines both CSF drainage and neuroprotection afforded by use of hypothermia.

Furthermore, prior art does not address stress related factors after injury to the brain. Because of the lack of specificity in mechanism of action, stress related factors are not down-regulated in a specific way using existing methods. What is required is a method that specifically modulates cortical-hypothalamic-pituitary-adrenal axis implicated in stress response, in a manner, that blunts the detrimental effects of stress related factors.

Similarly, prior art does not address the stimulation of pain pathways in traumatic brain injury. What is required is a method that would down-regulate nociceptive (pain) pathways but up-regulates anti-nociceptive pathways in the brain.

Prior use of hypothermia to prevent spinal cord injury has demonstrated clear benefits but there are methodological drawbacks limiting application of this approach in patients. In the spinal cord, regional spinal cord hypothermia increases spinal cord ischemia tolerance as disclosed by Meylaerts SA, De Haan P, Kalkman CJ, et al., in an article entitled "The influence of regional spinal cord hypothermia on transcranial myogenic motor-evoked potential monitoring and the efficacy of spinal cord ischemia detection", published in J Thorac Cardiovasc Surg, vol. 118, pp. 1038-1045 (1999). Mild hypothermia attenuated the biphasic increase in CSF glutamate and corresponding development of neuronal damage after spinal cord ischemia in a study disclosed by Isikawa T, Marsala M., in an article entitled "Hypothermia prevents biphasic glutamate release and corresponding neuronal degeneration after transient spinal cord ischemia in the rat", published in Cell Mol Neurobiol, vol. 19, pp. 199-208 (1999). Others have described clinical benefits in patients after selective spinal hypothermia to prevent spinal cord ischemia as disclosed in articles by, Trowbridge C, Bruhn T, Arends B., in an article entitled "Selective deep spinal hypothermia with vacuum-assisted cerebral spinal fluid drainage for thoracoabdominal aortic surgery", published in J Extra Corpor Technol, vol. 35, pp. 152-155 (2003); and by Svensson LG, Khitin L, Nadolny EM, Kimmel WA., in an article entitled "Systemic temperature and paralysis after thoracoabdominal and descending aortic operations", published in Arch Surg, vol. 138, pp. 175-179 (2003). Clear benefits of epidural cooling was demonstrated by Cambria RP, Davison JK, Carter

C, et al., in an article entitled "Epidural cooling for spinal cord protection during thoracoabdominal aneurysm repair: A five-year experience", published in J Vasc Surg, vol. 31, pp. 1093-1102, (2000). However, most authors use CSF drainage and avoidance of hypotension to minimize spinal cord ischemia. The use of the CSF drainage had been validated in a work disclosed by Coselli JS, Lemaire SA, Koksoy C, et al., in an article entitled "Cerebrospinal fluid drainage reduces paraplegia after thoracoabdominal aortic aneurysm repair: results of a randomized clinical trial", published in J Vasc Surg, vol. 35, pp. 631-639, (2002). It has been shown that subdural and epidural infusion cooling produced localized spinal cord hypothermia concurrently with uniformly distributed pressure increases and can result in spinal cord ischemia, as disclosed by Meylaerts SA, Kalkman CJ, de Haan P, et al., in an article entitled "Epidural versus subdural spinal cord cooling: cerebrospinal fluid temperature and pressure changes", published in Ann Thorac Surg, vol. 70, pp. 222-227, (2000). What is therefore required is a method that combines hypothermia with CSF drainage and does not concurrently increase pressure in the subdural space.

Prior art has limited means to effect changes in cerebrospinal fluid and the acid-base balance in the brain. The fact that the closed system of CSF circulation is independent of atmospheric pressure allows venous volume and pressure to influence the overall pressure of the fluid. Methods implicating introduction of fluid into the CSF for the purpose of heat transfer would alter CSF volume, CSF pressure and could also alter acid-base balance of CSF as described in detail by Kazemi H, Johnson DC, in an article entitled "Regulation of cerebral spinal fluid acid-base balance", published in J Physiol Rev, vol. 66, pp. 953-1037 (1986). It has been shown using continuous monitoring of

cerebral acid-base balance and oxygen metabolism in the neurointensive care setting, that hypothermia rather than hyperventilation tends to improve cerebral acidosis and ischemia, as disclosed by Shiohara T, Nara I, Saruta K, et al., in an article entitled "Continuous monitoring of cerebrospinal fluid acid-base balance and oxygen metabolism in patients with severe head injury: pathophysiology and treatments for cerebral acidosis and ischemia", published in *Acta Neurochir Suppl (Wien)*, vol. 75, pp. 49-55, (1999). Furthermore, it has been suggested that mild hypothermia could be beneficial in the prevention of severe encephalopathy in animal models of acute liver failure as a consequence of ammonia-induced impairment of brain energy metabolism as disclosed by Chatauret N, Rose C, Therrien G, Butterworth RF., in an article entitled "Mild hypothermia prevents cerebral edema and CSF lactate accumulation in acute liver failure", published in *Metab Brain Dis*, vol. 16, pp. 95-102 (2001). The choice of physiologic solution used for hypothermia could have a profound effect on viability of hippocampal tissue, which are particularly vulnerable to hypoxic-ischemia cellular injury as disclosed by Ikonomic M, Kelly KM, Hentosz TM, et al., in an article entitled "Ultraprofound cerebral hypothermia and blood substitution with an acellular synthetic solution maintains neuronal viability in rat hippocampus", published in *Cryo Letters*, vol. 22, pp. 19-26, (2001). It is therefore desirable to have a device that could introduce specifically chosen constituents of physiological solution with the aim of altering acid-base balance to desirable levels, and at the same time positively altering cerebral perfusion.

Prior art may be difficult to implement in patients with subarachnoid hemorrhage (SAH). Animal models of severe SAH show significant mean apparent diffusion

coefficient (ADC) changes calculated from diffusion-weighted magnetic resonance images, which are reversible by application of moderate hypothermia even when it is induced after a 60-minute delay. These findings support the concept of moderate hypothermia exerting a neuroprotective effect in severe SAH as disclosed by Piepgras A, Elste V, Frietsch T, Schmiedek P, et al., in an article entitled "Effect of moderate hypothermia on experimental severe subarachnoid hemorrhage, as evaluated by apparent diffusion coefficient changes", published in *Neurosurgery*, vol. 48, pp. 1128-1134 (2001). What is required is the flexible method that could easily be implemented alongside other surgical measures in the early post-SAH period.

Recent evidence suggest that mild hypothermia can alter cerebral vasoreactivity, and may enhance volatile anesthetic-induced vasodilatation of cerebral vessels as disclosed by Inoue S, Kawaguchi M, Kurehara K, et al., in an article entitled "Mild hypothermia can enhance pial arteriolar vasodilatation induced by isoflurane and sevoflurane in cats", *Crit Care Med*, vol. 30, pp. 1863-1869, (2002). What is required is a hypothermic device that could be integrated in the early and late surgical management of patients after SAH to prevent vasospasm without exposure to the risk of rebleeding in the early post-SAH period.

In the newborn, hypoxic-ischemic encephalopathy (HIE) remains one of the most important neurologic complications. Several experimental and clinical studies have shown that hypothermia is the most effective means known for protecting the brain against hypoxic-ischemic brain damage. Furthermore, recent data have suggested that platelet-activating factor (PAF) could play a pathophysiologically important role in the progression of hypoxic-ischemic brain injury as disclosed by Akisu M, Huseyinov A,

Yalaz M, et al., "Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia", published in Prostaglandins Leukot Essent Fatty Acids, vol. 69, pp. 45-50, (2003). What is required is a device adaptable for use in neonatology that could be selectively applied to the head to cool the cerebrospinal fluid in the ventricles through the anterior or posterior fontanelle.

SUMMARY OF THE INVENTION

The object of the present invention is to provide an improved patient temperature control system and method by apply cooling/rewarming to the CSF compartment, and is hereby referred to as cisternohypothermia.

Another object of the present invention is to apply cooling/rewarming directly to the CSF in the ventricles by allowing heat transfer to occur by mixing of cooling/rewarming solution introduced through a ventricular catheter with CSF. This method is referred to as invasive 'direct internal cisternohypothermia'.

Another object of the present invention is to apply cooling/rewarming to the CSF in the ventricles by allowing heat transfer to occur between the CSF and cooling/rewarming solution flowing in a blind loop ventricular catheter. This method is referred to as invasive 'indirect internal cisternohypothermia'.

The present invention provides a method and apparatus for selectively cooling the brain to reduce the risk of brain injury from accidental medical conditions or planned clinical procedures, and allows for selective cooling of the brain independent of core body temperature by invasive internal cooling of CSF in the cisterns of the brain.

The present invention includes steps of selectively controlling cerebral

autoregulation by altering CBF and CPP; and cerebral vasoreactivity by altering ICP and MABP, accomplished by selectively altering CSF temperature and CMR, to further reduce the damage caused by brain injury in various accidental medical conditions or planned medical procedures.

The present invention could be specifically applied to maintain hypothermia and hence prevent hyperthermia in the brain during the rewarming phase of procedures requiring hypothermia of core temperature such as in cardiopulmonary bypass (CPB) surgery or liver transplant surgical procedures.

The present invention has an added advantage for selective cooling of the brain while minimizing the risk of frostbite, pneumonia or other thermal injury to the patient being cooled.

The invention is particularly advantageous in cardiac surgery, where it could be possible to employ normothermic CPB in patients undergoing coronary artery bypass grafting (CABG) or repair of intracardiac anomalies, with reduced risk exposure to ischemic neurologic sequelae.

The special embodiment of this invention is illustrated in the specifications, it includes block and schematic diagram for the format of the instrumentation, and how the system functions is shown by way of example. The human involved will be referred to as "patient" by way of example.

These and other objects of the invention may become more apparent to those skilled in the art upon reviewing the description of the invention as set forth hereinafter, in view of its drawings.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. 1 shows the mechanism of transfer of heat to the CSF.

FIG. 2 shows the CSF pulsatile flow pathways as a means of heat exchange throughout the brain and spinal cord.

FIG. 3 shows the regulatory centers in their anatomic relationship to CSF pathways implicated in heat exchange.

FIG. 4 shows another embodiment of the present invention adapted for placement in the intracranial ventricles for drainage and internal cisternohypothermia.

FIG. 5 shows the use of the double barrel catheter introducer held in preparation for insertion of the double barrel catheter into the ventricle.

FIG. 6 shows the sequential insertion of the catheter introducer into the heat exchange catheter of the "double barrel" catheter before placement into the ventricle.

FIG. 7 shows the sequential release of the "double barrel" catheter from the introducer into the ventricle.

FIG. 8 shows the preferred embodiment of the setup of the double barrel catheter within the ventricle.

FIG. 9 shows an exemplary setup of the heat exchange procedure using the double barrel catheter in one embodiment of the present invention.

FIG. 10 shows another embodiment of the present invention as a loop catheter for internal cisternohypothermia.

FIG. 11 shows an exemplary setup of the heat exchange procedure using the loop catheter in one embodiment of the present invention.

FIG. 12 shows a schematic diagram of interconnected devices in an intensive care setting with the present invention.

FIG. 13 shows the program flow chart of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

FIG. 1 shows the mechanism of transfer of heat to the CSF. As mentioned above, the method of application of cooling to lower the temperature of the CSF is hereby referred to as "cisternohypothermia". Such a system *1* (cisternohypothermia) would have direct thermal exchange with the CSF compartment *2* cooling the CSF bathing the neural tissue and altering cerebral metabolism *3* by reducing cerebral metabolic rate in neural cells, thereby conserving energy stores in cells. This will alter the balance between heat gain and heat loss, and following purely physicochemical considerations; however, this will also ultimately reset the thermoregulation *4* by direct effects on neurons of central and peripheral afferents to the preoptic hypothalamus. There is a culminative effect of reduced metabolic heat production *5* and further cooling of the CSF and blood. The heat loss effect on the physical fluid characteristics of the CSF would cause a decreased CSF volume *6* and hence reduced intracranial pressure *10*. During CSF pulsatile flow, heat exchange occurs with the cerebrovascular system and alters cerebral blood flow *7* resulting from the cooling effect and there would be reduction in cerebral blood volume *8* via reflex vasoconstriction *9* analogous to "cold pressor effect" the cerebral perfusion pressure would rise. There is an overall benefit of decreased CSF volume *6* and decreased intracranial pressure *10* preserved vasoreactivity and autoregulation. The present invention would permit the use of hypothermia to desirably alter the major indices of cerebral autoregulation as disclosed by Rosner M. in an article entitled "Pathophysiology

and management of increased intracranial pressure", in a book by Andrews BT. (ed.) entitled "Neurosurgical intensive care", published by McGraw Hill Inc., New York, pp. 57-112 (1993).

FIG. 2 shows the CSF pulsatile flow pathways as a means of heat exchange throughout the brain and spinal cord. The ventricles of the brain, the narrow spinal canal and the subarachnoid space are filled with CSF. CSF therefore baths both the inner and outer surfaces of the brain and cord. It is a colorless liquid containing a few lymphocytes. Its composition differs from plasma in that it contains very little protein and has lower concentrations of K^+ , Ca^{2+} and phosphate, but higher concentrations of Cl^- . The glucose content is slightly lower and it is slightly more acidic (about 0.1 pH units) than plasma. Most of the components of CSF are secreted, some (for example Na^+) by active transport mechanisms, from the vascular plexus (the chorioid plexuses) lining the lateral and third ventricles CSF is formed at the rate of 0.3 ml/min or 500 mL/day in man, and its total volume is about 100-160 mL, making a renewal of the fluid every 4-5 hours. CSF pressure varies between 50 - 180 mmH₂O, depending on posture and the level of the neuraxis at which the pressure is measured. After a brain injury, there is alteration in CSF formation rate and a change in chemistry that could promote cellular injury. According to the teachings of the present invention, a means is provided to alter the chemistry of the CSF and promote neuronal viability. The cooling effect of CSF would spread to the entire brain through the pulsatile flow of CSF in the cisterns. The CSF flows from the lateral ventricles *11*, through foramen of Monro *12*, into the third ventricle *13*, and via aqueduct of Sylvius *14* into the fourth ventricle *16*. This region of the periaqueductal central gray area has been implicated in physical and emotional pain. The flow of cold CSF through

the periaqueductal central gray area according to the teachings of the present invention reduces the stimulation of this subcortical region and could positively regulate responses to physical and psychological pain. Furthermore, CSF flow ensures that other vital brain stem area are cooled. Between the roof of the fourth ventricle and the cerebellum lies the cisterna ambiens *15*. The communication between the ventricular and subarachnoid fluids in by way of three foramina; a medial opening in the roof of the fourth ventricle, the foramen of Magendie, establishes a communication with the large cerebello-madullary cistern, the cisterna magna *17*. The lateral recesses of the fourth ventricle wind around the medulla, passing over the base of the inferior cerebellar peduncle; these recesses open to the subarachnoid space *18* on the basal aspect of the brain as the foramina of Luschka. Each foramen is situated in the angle between the pons and medulla, and opens into the cisterna pontis *20* on the basal aspect of the brain stem. The CSF circulates to the lumbosacral region *19* in a bulk flow model. However, the rapid heat exchange could be explained by large pulsatile flow originating from the 'thalamic' or 'third ventricular' pump and as proposed by DuBoulay G, O'Connell J, Currie J, et al ., disclosed in an article titled "Further investigations on pulsatile movements in the cerebrospinal fluid pathway", published in *Acta Radiologica*, vol. 13:, pp. 496-523 (1972). The CSF pulsatile movement that is dependent on the systolic and diastolic times of vascular pulsation has been documented using magnetic resonance imaging by Njemanze PC, Beck OJ, disclosed in an article titled "MR-Gated intracranial CSF dynamics: evaluation of CSF pulsatile flow", published in *AJNR*, vol. 10, pp. 77-80 (1989). The flow of CSF passes to other cisterns: cisterna interpeduncularis *21*, cisterna chiasmatica *22*, and cisterna frontalis *23*. Heat exchange occurs with the cerebral venous sinuses: including the

superior sagittal sinus **24**, sinus rectus **25**, and great vein of Galen **26**. Establishing the presence of sustained pulsatility of the CSF flow using MR-gated intracranial CSF dynamics method in patients, particularly those with normal pressure hydrocephalus would be a prerequisite for spread of the cooling effect when using the present invention.

FIG. 3 shows the regulatory centers and their anatomic relationship to CSF pathways implicated in heat exchange. In a neutral environment, the metabolic rate of humans consistently produces more heat than is necessary to maintain core body temperature at 37 degrees Celcius. The hypothalamus (HT) **27** is the center of body temperature control. Neurons in both the preoptic anterior and posterior hypothalamus receive two kinds of signals - one from peripheral nerves that reflect receptors for warmth and cold and the other from the temperature of blood and CSF bathing the region. These two signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature as disclosed by Gelfand JA., Dinarello CA, Wolf SM., in an article titled "Fever, including fever of unknown origin", in a book by Isselbacher K. J., et al. (editors), entitled "Harrison's Principles of Internal Medicine", 13th Edition, published by McGraw-Hill Inc., New York: p. 82 (1994). These central afferent signals could be altered by the temperature of CSF bathing the region of hypothalamus **27** and that of blood flowing via cerebral sinuses (transverse sinus, straight sinus **25**, sagittal sinus **24** and vein of Galen **26**), and furthermore via CSF pulsatile movement in the ventricles (lateral **11**, third **13** and fourth **16**), cisterna magnum **17** and basal cisterns **20-23**. With the new, lower "thermostatic setting," signals go to various efferent nerves, particularly those sympathetic fibers innervating the peripheral blood vessels, which in turn initiate vasodilatation and promote heat loss. The hypothalamic thermoregulatory

centers also sends signals to the cerebral cortex, particularly to centers that integrate the levels of emotional stress and cognition such as the central cingulate (CC) 28 and anterior cingulate (AC) 29; to the pituitary gland 30 to modulate the stress axis; as well as centers implicated in modulating the level of physical pain (anti-nociception) such as dorsomedial thalamus (DMT) 31 forming the walls of the third ventricle 32 and the periventricular central gray area including areas around the aqueduct of Sylvius 33 and fourth ventricle 34 as disclosed by Panksepp J., in an article titled "Feeling the pain of social loss," published in Science, vol. 302, pp. 237-239 (2003). Using temperature modulation and altering of activation patterns at these centers, it is thought that the level of post-traumatic stress syndrome and physical pain associated with traumatic head injury could be modulated using hypothermia according to the teachings of the present invention. There is mounting evidence that mild alterations in brain temperature can have a significant effect on functional outcome and histopathology following cerebrovascular accidents. In these studies, improvement in outcome was reported with mild hypothermia and worsened with mild hyperthermia. Modulation of ischemic brain injury by small alterations in brain temperature has been discussed. Temperature changes of either 1 or 2 degrees Celcius altered functional and histologic outcome in a canine model of complete cerebral ischemia, as disclosed by Wass CT., et al. in an article titled "Temperature changes of ≥ 1 degree C. altered functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia" published in Anesthesiology, vol. 83, pp. 325-335 (1995). Similarly, Warner DS., et al. disclosed in an article titled "Sevoflurane and halothane reduce focal ischemic brain damage in the rat: Possible influence in thermoregulation," published in Anesthesiology, vol. 79, pp. 985-992

(1996), discovered that a change in brain temperature of 1.2.degree Celcius altered functional and histologic outcome in a rat model of focal cerebral ischemia. Although the exact mechanism remains to be elucidated, there is evidence that such changes can have a significant effect on functional outcome and histopathology following cerebral ischemia.

FIG. 4 shows another embodiment of the present invention adapted for placement in the intracranial ventricles for drainage and internal cisternohypothermia. There are two catheters that could be physically joined together on a firm polypropylene base, and implanted into the ventricle through a burr hole or twist drill. A design in which both catheters are joined to form a double lumen catheter, in which one lumen is for drainage and the other for heat exchange, is hereby referred to as "double barrel" ventricular catheter. The two catheters, one is similar to a conventional intracranial ventricular catheter usually made of silicon elastomer tubing impregnated with white barium sulphate to provide radiopacity, with a proximal end, a mid portion and a distal end with perforated holes. As is conventionally accepted, black length markers made of a graphite-impregnated silicon elastomer are positioned on the catheter at points 5, 10, 15 cm from the proximal tip to enable the surgeon to gauge the depth of the penetration of the catheter into the lateral ventricle. There is a right angle clips 38 designed to angulate the catheter so it may lie within the mid portion of the lateral ventricle. The catheter is joined to the cooling catheter by a relatively firm polypropylene plate 39 incorporated in the catheter design to provide some rigidity and resistance to catheter kinking, and is a heat insulator. The second heat exchange catheter provides cooling of the CSF by introducing a cold physiologic solution of known constituents into the CSF compartments at a predetermined rate. The heat exchange catheter has a proximal end 40 that connects to

the source of cold fluid, a mid portion **41** and a distal portion with four slit openings **42** at 90 degrees in the catheter wall near the distal tip. These slit openings are designed to provide protection from retrograde flow and occlusion of the catheter. There is a right angle clip **43** that is designed to angulate the catheter so that the proximal portion **40** is turned away from the proximal end of the other ventricular drainage catheter **35**.

FIG. 5 shows the use of the double barrel catheter introducer held in preparation for insertion of the double barrel catheter into the ventricle. This disposable quick release ventricular introducer has a stylet grip **44** for holding, a silicon tube "spring" **45**, a shaft grip **46**, a stainless steel shaft **47** which covers the main stainless steel stylet **48**. The blunted tip of the stainless steel stylet is used for insertion into the slit hole **42** of the catheter in preparation for introduction into the ventricle.

The ventricular introducer is held usually between the thumb **49** and the index **50**, and third fingers. For use with the double barrel catheter, the catheter introducer is held between the first, second and third fingers on one hand like a Chinese chopstick. The tip is inserted into the slit opening or perforated hole of one catheter, and both catheters with the introducer are held firmly together like a pair of Chinese chopsticks. A suitable ventricular catheter introducer could be obtained from Pudenz Schulte Medical, Santa Barbara California.

FIG. 6 shows the sequential insertion of the catheter introducer into the heat exchange catheter of the double barrel catheter, before placement into the ventricle. The introducer tip is inserted into the heat exchange catheter slit opening **42** or by introduction into the perforated hole **37** of the drainage catheter in a similar manner. The

catheter introducer along with the double barrel catheters are introduced into the ventricle.

FIG. 7 shows the sequential release of the double barrel catheter from the introducer into the ventricle. The introducer is held firmly at the stylet grip **44** between the thumb, index finger **50** and third finger of one hand and withdrawn with the first **51** and index finger **52** of the other hand. A swift action that pulls back the stylet grip **44** by about 1.5 cm assures release of the catheter into the ventricle. The introducer is now withdrawn from the ventricle.

FIG. 8 shows the preferred embodiment of the setup of the double barrel catheter within the ventricle. The right angle clips **38** and **43** are used to bend both catheters to 90 degrees in opposite directions at the point where they exit the twist drill or burr hole. They use of the clips for this purpose is optional. The right angle clip **38** is secured to the adjacent tissue by passing sutures through the two suture flanges on the sides of the clip **54**. The extracranial portion **55** of the ventricular catheter is connected to the CSF-flow control valve **56**, with markings showing low pressure (one dot) and direction of flow (arrow head) **57**, by way of example. The supply line **58** with cooling fluid **59** is connected to the cooling catheter at the proximal end **40**.

FIG. 9 shows an exemplary setup of the heat exchange procedure using the double barrel catheter in one embodiment of the present invention. The proximal ends of the double barrel catheter **62** protruding from the burr hole **60** are connected to the CSF-flow control valve **63**, which is in turn connected to the peritoneal catheter. The heat exchange catheter proximal portion **40** is connected to an infusion system comprising a fluid line **65**, containing cold physiologic solution **66**, hanging from an IV stand **67**,